# EXHIBIT L

**UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF DELAWARE**

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| IN RE: '318 PATENT INFRINGEMENT LITIGATION | Civil Action No. 05-356-KAJ (Consolidated) |

**SECOND EXPERT REPORT OF DR. HOWARD M. FILLIT**

## I. INTRODUCTION

1. This report supplements my opening expert report of July 28, 2006. In this report, I was asked by Plaintiffs to review the opinions set forth in the reports by Drs. Edward Domino and Allan Levey in this case and to set forth my own opinions concerning the validity of U.S. Patent No. 4,663,318 ("the '318 patent") in view of the defendants' claims that the patent is invalid due to anticipation, obviousness, or lack of enablement.

2. In forming the opinions set forth in this report, I have relied upon my experience and knowledge of the relevant literature and state of the art and reviewed the Domino and Levey reports, the documents discussed in those reports, and the materials referenced in my opening report and in Exhibit A to this report.

## II. LEGAL STANDARDS

3. In order to assist me in evaluating the defendants' experts' reports and in forming my own opinion concerning the validity of the patent, I have been informed of the legal standards governing anticipation, obviousness, and enablement.

### A. Anticipation

4. I have been informed that the statutory requirement for anticipation of a patent claim is that the claimed invention must be shown to be "known or used by others in this

country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent." 35 U.S.C. § 102(a). Defendants' experts have asserted that the '318 patent was anticipated by an article published before Dr. Davis applied for her patent – P.A. Bhasker, "Medical Management of Dementia," The Antiseptic, 71: 45-47 (1974) (the "Bhasker article"). In order for that article to anticipate claims 1 and 4 of the '318 patent, I understand that this article must describe the invention claimed in those patent claims. That is, the article must describe, to one of ordinary skill in the art, each and every element of those claims.

5. Moreover, in order for the article to qualify as a "printed publication," I understand that the Bhasker article must be "publicly accessible." That is, it must be accessible to persons skilled or interested in the art. I understand that indexing of the article is relevant to determining whether it was accessible to persons skilled or interested in the art.

**B. Obviousness**

6. I have been informed that the following factors are relevant in determining whether a patent is invalid for reasons of obviousness: (1) the scope and content of the prior art; (2) the differences between the patented invention and the prior art; (3) the level of ordinary skill in the art; and (4) objective considerations of non-obviousness. I note that objective considerations of non-obviousness were addressed in my opening report. In forming my opinion, I have also been asked to consider whether the prior art would have provided a person of ordinary skill a motivation to combine or modify the prior art references so as to arrive at the claimed invention and also whether it would have provided such a person with a reasonable expectation of success in doing so.

C. **Enablement**

7. I understand that to be valid, a patent must enable one skilled in the art to make and use the claimed invention. A patent is enabling even if some experimentation is required, as long as it is not unduly extensive.

## III. LEVEL OF ORDINARY SKILL IN THE ART

8. In forming the opinions expressed in this report, I have used the level of skill proposed by Drs. Domino and Levey, namely, "an M.D. or Ph.D. interested in the field of Alzheimer's disease research ... who, as a result of such training and/or interest, would have knowledge of the cholinergic hypothesis of Alzheimer's disease, the role of acetylcholine in memory, and pharmacological strategies and approaches for treating Alzheimer's disease and related dementias." (Domino ¶ 30; Levey ¶ 19). As a medical doctor actively engaged in Alzheimer's research in January 1986, I believe I would meet this definition, and I worked closely with others who would too. I believe I have a good understanding of the knowledge and thinking of such a person at that time.

9. I note, however, that in my opinion, the level of skill deemed "ordinary" by Drs. Levey and Domino is overstated. At the time, Alzheimer's research was a specialized field. The "ordinary" person interested in methods of treating Alzheimer's disease – who I assume would be the relevant readership for Dr. Bonnie Davis's patent on using galantamine to treat that disease – would have been a treating physician. In 1986, such a person would not likely have had experience with Alzheimer's research. However, for purposes of forming the opinions expressed in this report, I have used the level of skill set forth in the reports of Drs. Levey and Domino, because the difference does not alter my conclusions.

## IV. ANTICIPATION

10. I disagree with the assertions contained in Drs. Levey's and Domino's reports that the Bhasker article anticipates the claims of the '318 patent. In my opinion, these assertions rely upon a wholly unreasonable reading of the Bhasker article, which in fact teaches that "progressive dementias" – a category that Drs. Levey and Domino treat as encompassing AD – are untreatable. Bhasker at p. 45 ("With regard to progressive dementia, there appears very little to offer. Only management and no treatment is possible.").

11. The Bhasker article's single reference to galantamine (along with neostigmine) appears in connection with treating "local brain damage like tumour, head injury, infarct, etc." (p. 46). AD is not a form of local brain damage like tumour, head injury, infarct, or the like. A clinician or Alzheimer's researcher would read Bhasker as suggesting galantamine for forms of local brain damage. He or she would not understand the article to be suggesting galantamine for AD.

12. This understanding of the Bhasker article would be reinforced by the article's reference to the work of Dr. Alexander Luria. Dr. Luria was a Soviet neurologist known for his work in treating neurological disorders associated with tumor or local brain injury (that is, traumatic encephalopathy). I am not aware that he ever studied Alzheimer's disease; an ordinary clinician or Alzheimer's researcher would certainly not have thought of him in connection with such work. Instead, Bhasker's reference to Luria would have underscored to the skilled reader that the article's reference to galantamine was made in connection with local brain damage.

13. This understanding of the Bhasker article would also be reinforced by the fact that the Bhasker article refers jointly to galantamine and neostigmine in discussing the "deinhibitory process" said to be useful in treating local brain damage. It is true that galantamine was known to have certain therapeutic uses in common with neostigmine, such as "an antagonist of non-

depolarizing muscle relaxants." M. Bretagne, et al., "Essais Cliniques en Anesthesiologie d'un Nouvel Anticholinesterasique la Galanthamine," Anesthesie Analgesie Reanimation, 1: 285-92 (1971) (Translation at JAN RAZ 134055). Thus, the Bretagne reference finds both galantamine and neostigmine useful in reversing the paralyzing effects of curare. However, as a quaternary ammonium derivative, neostigmine does not pass the blood-brain barrier, a limitation that one of ordinary skill would have recognized in 1986. For this reason, neostigmine would be recognized as useless for improving cholinergic activity within the brain: "Having a quaternary ammonium group, [neostigmine] cannot penetrate the blood-brain barrier and is therefore useless in combating the central effects of anticholinergic drugs." D.A. Cozanitis, "Galantamine Hydrobromide, A Longer Acting Anticholinesterase Drug, in the Treatment of the Central Effects of Scopolamine (Hyoscine)," Anesthetist, 26: 649-50 (1977), at p. 650. Hence, Bhasker's reference to using either neostigmine or galantamine for "deinhibition" could not reasonably have been read as referring to any central cholinergic effect, since neostigmine was known not to have any central effects. This would necessarily exclude treatment of conditions, such as AD, which are wholly central in nature.

14. In short, it is my opinion that no skilled reader of the Bhasker article would reasonably understand the article to suggest galantamine for AD.

15. In addition, I do not believe a reader of ordinary skill would have understood the Bhasker article to reference AD at all. The article divides dementia into two types – reversible and irreversible (or progressive). Needless to say, the former category does not include Alzheimer's disease: there is not a single case in the 100 years since the disease was first identified where Alzheimer's disease has been reversed – in fact, reversal of a patient's dementia

would disprove an initial diagnosis of AD. AD cannot fall within the category of "reversible" dementia.

16. As to the latter category of irreversible dementias, the Bhasker article states that "[t]he irreversible cases belong to the category of dementias where there is a progressive fall-out of neurons and the course of the illness is rapidly downhill." (p. 45). AD may progress steadily and relentlessly, but its course is not rapid. Quite the reverse, the disease often runs for more than a decade after first diagnosis before final demise. I do not believe any reasonable clinician or researcher in Alzheimer's disease would have described the course of AD in 1986 as "rapidly downhill" and similarly would not have understood Bhasker's reference to "irreversible" dementias with a rapid downhill course to encompass Alzheimer's disease. Instead, such a reader would have concluded that the Bhasker article simply does not address AD.

17. Dr. Levey suggests that any reference to irreversible dementias "necessarily includes the most prevalent of the irreversible dementias, Alzheimer's disease." (Levey ¶ 99). But that ignores both the time and place of the Bhasker article. While AD may now be recognized as the most prevalent form of dementia in the elderly, that recognition was only beginning to emerge in 1974, when the Bhasker article was published. It would have been entirely natural for an article published at that time to overlook AD. Indeed, I graduated from medical school in 1974, and as best I recall, I was not taught anything about the disease in school.

18. Moreover, recognition of Alzheimer's Disease was particularly slow to come in India, where the Bhasker article was written and published. At the time, and continuing to the present day, Alzheimer's disease is rarely diagnosed in India. As recently as the mid-1990s, I was asked to consult on an elderly patient, in India, who was suffering from mental confusion,

and I was flown to India for that purpose because of the lack of experience or expertise in India with diagnosis in senile dementia or Alzheimer's disease. A person of ordinary skill reading a 1974 article on dementia written and published in India would not be at all surprised that Alzheimer's disease was not addressed.

19. In this regard, it is worth noting that the Bhasker article is published in a journal entitled The Antiseptic. Authors typically select journals in which to publish on the basis of subject matter and readership. Alzheimer's disease has nothing to do with microbial infection; its treatment does not involve antiseptics or antimicrobials.

20. In addition, the Bhasker article was not accessible to persons of ordinary skill in the art in 1986. The journal in which it appeared, The Antiseptic, is not a reference that researchers in the Alzheimer's field (let alone treating physicians with an Alzheimer's patient) would have reviewed in the ordinary course.

21. Moreover, a researcher working in Alzheimer's drug development in 1986 would not have found the Bhasker article through the normal channels of scientific research. Such a researcher would have used a medical index and would have reviewed the relevant, standard scientific journals. These techniques would not have led a researcher in Alzheimer's disease, much less a clinician, to find the Bhasker article. In 1986, the standard index – the Index Medicus, a monthly guide to articles published in approximately 4,000 journals – did not include The Antiseptic. And as far as I am aware, the Bhasker article was not cited by any relevant scientific literature at the time.

22. Finally, the title of the journal would itself further discourage finding the article. A person of ordinary skill searching for articles concerning either galantamine or Alzheimer's disease would be highly unlikely to look in a journal entitled The Antiseptic. As noted,

Alzheimer's disease does not involve microbial infection. Galantamine is not an antiseptic or antimicrobial. Given the vast amount of literature published in journals potentially bearing on a pharmacologic investigation of Alzheimer's disease, I cannot imagine that a clinician or Alzheimer's researcher seeking a treatment of Alzheimer's disease would have had any occasion to review The Antiseptic. Despite working for 25 years in the Alzheimer's field, during which time I reviewed thousands of articles in hundreds of journals, I had never seen nor heard of The Antiseptic until this litigation.

## V. NON-OBVIOUSNESS

### A. Differences between the prior art and the patented invention

23. I understand that in reaching a conclusion about obviousness, the relevant inquiry is to compare the disclosures in the prior art, as they would be understood by one of ordinary skill in the art, to the claims of the patented invention. Those claims are described in my opening report. (See Fillit Report ¶¶ 19-23).

24. I believe that the invention claimed in the '318 patent differs from the prior art, as it would be understood by a person of ordinary skill, in at least two ways. First, the art as of January 1986 did not describe any drug as being a therapeutically effective method of treating Alzheimer's diease. Second, the art did not describe galantamine as a method for treating Alzheimer's disease.

25. I understand the reports of Drs. Domino and Levey to assert that physostigmine and tacrine had been shown by 1986 to be therapeutically effective treatments for Alzheimer's Disease. Dr. Levey goes so far as to assert that "[o]nce the physostigmine trials were known, it is not an exaggeration to say that it would have been obvious to anyone reading the literature that the ideal drug candidate for treating Alzheimer's disease would perform like physostigmine, but

without the drawbacks." (Levey ¶ 36). I find this an astonishing statement, one that is completely contradicted by the facts.

26. In the first place, I was just such a person who was following the physostigmine and other Alzheimer's disease literature in January 1986. Yet, not only was it not obvious to me that a drug like physostigmine would work, to the contrary I believed that the cholinesterase inhibitor approach was not working. In October 1985, I and several co-workers submitted a paper, published in 1986, in which we observed that acetylcholine precursor and cholinesterase inhibitor approaches to correcting the cholinergic deficit in AD had, for the most been "been unsuccessful or equivocal." H. Fillit, et al., "Observations in a Preliminary Open Trial of Estradiol Therapy for Senile Dementia-Alzheimer's Type," Psychoneuroendocrinology 11(3): 337-45 (1986), at p. 337. In addition, while we noted that "some benefit has been ascribed to cholinesterase inhibitors," those compounds "are limited by their low therapeutic ratio." (p. 337). Accordingly, we suggested estradiol as an alternative approach, which we believed looked promising in light of testing we had done on seven female patients with Alzheimer's Disease. Yet, even here, we warned not to draw any firm conclusions about efficacy, and we cautioned that "controlled clinical trials are needed to further define the potential therapeutic role for estradiol in postmenapausal women with SDAT." (p. 343).

27. The fact that we were proposing estradiol as "[a]n alternate approach to modifying this central cholinergic deficit" in AD, and actually testing it on Alzheimer's patients (p. 337), demonstrates that it was not obvious to us that a cholinesterase inhibitor approach was a therapeutically effective strategy for treating Alzheimer's Disease, let alone – as Dr. Levey would have it – that a cholinesterase inhibitor was "the ideal drug candidate for treating Alzheimer's disease." (Levey ¶ 36).

28. Nor was I alone in my skepticism of cholinesterase inhibitors. As I discussed in my opening report, there was considerable skepticism in the Alzheimer's field at the time of a cholinesterase inhibitor approach to treating the disease. Indeed, the many clinical trials conducted of other approaches, including muscarinic agonists and metabolic enhancers, demonstrates clearly that many in the field did not view cholinesterase inhibitors as the right aproach.

29. Even the articles Drs. Domino and Levey cite in support of their assertions do not describe cholinesterase inhibitors as therapeutically effective. For example, in R. Mohs, et al., "Studies of Cholinergic Drug Effects on Cognition in Normal Subjects and Patients with Alzheimer's Disease," Aging 17: 225-30 (1981), the authors conclude to the contrary that "[a]t present it is not clear whether studies of cholinergic drugs will lead to useful treatments for any of the debilitating dementias that afflict so many people." (p. 229). And in R.C. Mohs, et al., "Clinical Studies of the Cholinergic Deficit in Alzheimer's Disease," J. Amer. Geriatrics. Soc. 33(11): 749-57 (1985), the authors again express skepticism that a cholinergic approach such as a cholinesterase inhibitor would prove clinically beneficial:

> Combining careful biologic assessment and clinical diagnosis with attention to the unique pharmacologic properties of cholinergic drugs may ultimately identify a group of AD/SDAT patients who can derive meaningful clinical benefit from cholinesterase inhibitors or choliergic agonists. However, it must be recognized that even when these conditions are met, the use of such drugs could be severely limited. It has been pointed out, for example, that cholinergic cells have relatively few postsynaptic projections that are nonoverlapping, so that it is difficult for surviving cholinergic cells to compensate functionally for lost cells by increasing their firing rate. In addition, none of these drugs may be able to duplicate the phasic action of cholinergic cells in transmitting information. If such considerations prove to be true then any pharmacotherapy of AD/SDAT may have to depend on manipulation of transmitters and cotransmitters operating at sites postsynaptic to the dying neurons. (p. 756)

30. To similar effect is: B.S. Greenwald, et al., "Neurotransmitter Deficits in Alzheimer's Disease: Criteria for Significance," J. Amer. Geriatrics Soc., 31(5): 310-16 (1983):

"while it is generally agreed that L-dopa and other agonists can ameliorate symptoms in [Parkinson's Disease] patients, the effects of cholinergic-enhancing compounds in AD are much more limited. Encouragingly, positive effects of cholinomimetics have been reported; however, a level of clinical utility has not been achieved." (p. 313) And C. Johns, et al., "The Cholinergic Treatment Strategy in Aging and Senile Dementia," Psychopharmacology Bulletin, 19(2): 185-197 (1983): "The success of cholinomimetic treatment strategies thus far has been modest, and definitive treatment of SDAT awaits clarification of complex neurochemical variables, delineation of parameters that can predict response, and development of appropriate safe, long-acting pharmacologic agents." (p. 193).

31. In my opinion, a person of ordinary skill in the art would not understand the articles cited by Drs. Levey and Domino to be describing a cholinesterase inhibitor strategy generally or any particular cholinesterase inhibitor specifically as therapeutically effective for the treatment of Alzheimer's disease. This is confirmed, in my opinion, by the prevailing skepticism of cholinesterase inhibitors at the time and the preference for other approaches, as I reviewed in my opening report.

**B. Motivation to Combine**

32. In my opinion, the prior art also did not provide a person of ordinary skill in the art with the motivation to combine the references so as to conclude that galantamine could be a treatment for Alzheimer's disease. In addition to the limitations in the prior art concerning the cholinesterase inhibitors physostigmine and tacrine outlined above, the pharmacologic properties of galantamine known at the time would have made it appear unsuitable for use in treating Alzheimer's disease. Certainly, it would have appeared less suitable than physostigmine or tacrine, which were viewed as flawed, as Dr. Domino acknowledges. (E.g., Domino ¶ 43 ("it

was also recognized that physostigmine's and tacrine's usefulness as a long-term treatment for Alzheimer's disease was limited by its pharmacology")).

33. Galantamine is very different chemically from physostigmine and tacrine, with a different molecular structure. (See Domino ¶ 39). Such differences in the chemistry and molecular structure between drug substances can impact their pharmacologic properties, as a person of ordinary skill would recognize. In the case of galantamine and physostigmine, differences in their chemical structures would have cast much doubt on the simple substitution of one for the other.

34. In addition to these differences in chemistry, galantamine is a much weaker cholinesterase inhibitor than physostigmine, tacrine, or other cholinesterase inhibitors. Several researchers had made rough calculations of galantamine's relative potency by the time of the '318 patent application. In 1962, Boissier and Lesbros published an article in which they calculated that galantamine hydrobromide was 400-1000 times less active than neostigmine. J. Boissier and J. Lesbros, "La galantamine, puissant cholinergique naturel. II-Activite anticholinesterasique de galanthamine et de quelques derives," Ann. Pharm. Fr. 2: 150-55 (1962) (Translation at SYN RAZ 0022935). In 1965, Nesterenko measured the relative potencies of physostigmine and galantamine, and concluded that doses of galantamine needed to to 10-12 times higher than for physostigmine to achieve similar levels of cholinesterase inhibition. L.N. Nesterenko, "Effect of Galantamine on the the Acetylcholinesterase Activity of Various Regions of the Brain," Farmakol. I Toksikol. 28(4): 413-14 (1965) (Translation at SYN RAZ 0013374). And, finally, in 1976, Tonkopii et al. compared the action of galantamine and tacrine on acetylcholinesterase from human erythrocyte and from brain slices of various animals, and they concluded that galantamine was about 100 times weaker against acetylcholinesterase than

physostigmine. V. D. Tonkopii et al., "Interaction of Reversible Inhibitors with Catalytic Centers and Allosteric Sites of Cholinesterases." Bull. Exp. Biol. Med. 86: 400-01 (1976) (Translation at SYN RAZ 0013159).

35. Such calculations were not obscure: it was well-known in the scientific literature by 1986 that galantamine was a relatively weaker inhibitor of cholinesterase, as reflected by roughly contemporaneous publications: D.S. Paskov, "Galantamine," in D.A. Kharkevich (ed.) New Neuromuscular Blocking Agents, Vol. 79, Handbook of Experimental Pharmacology, pp. 653-72 (1986), at 654. ("The inhibitory effect of galanthamine on acetylcholinesterase . . . was found to be considerably lower than that of physostigmine and neostigmine."); D. Mihailova et al., "Modeling of Pharmacokinetic and Pharmacodynamic Behavior of Nivalin in Anaesthetized Cats," Methods Find. Exptl. Clin. Pharmacol. 11: 595-601 (1985) (noting the weakness of galantamine's anticholinesterase effect). Thus, it is my opinion that a person of ordinary skill in 1986 would have recognized galantamine's relatively weak potency.

36. This recognition of galantamine's weak potency would have discouraged drug developers from recognizing or developing it as a treatment for Alzheimer's disease. In fact, the literature expressed a concern that other cholinesterase inhibitors would not be effective because they were not potent enough – they did not achieve sufficient levels of cholinesterase inhibition. In 1985, Mohs et al., for example, expressed the view that high levels of cholinesterase inhibition correlated with beneficial results in the treatment of Alzheimer's disease. They wrote: "Improvement on memory tests while receiving physostigmine was highly correlated with the percent of inhibition in CSF: The patients who improved up to 40% on certain memory tests had a very high degree of cholinesterase inhibition, and patients with smaller improvements also had

a smaller percent of cholinesterase inhibition." R.C. Mohs et al., "Oral Physostigmine Treatment of Patients With Alzheimer's Disease," Am. J. Psychiat. 142: 28-33 (1985), at 32.

37. The weak potency of galantamine would have given rise to yet another concern discouraging its use for Alzheimer's disease: that any potentially therapeutic dose of galantamine would have serious safety and tolerability issues, because higher doses would need to be given in order to achieve efficacy. This concern would only have been increased by galantamine's established peripheral effects. The Pernov article cited by both Drs. Domino and Levey, K.G. Pernov, "Nivalin and its Curative Effect Upon Diseases of the Nervous System," Psychiatry, Neurology and Medical Psychology Bulletin on Research and Practice, 13(11)" 416-420 (1961) (cited at Domino ¶¶ 37, 87; Levey ¶¶ 81, 83, 103, 115-116), for example, describes galantamine as treatment for "**above all** diseases of the neuromuscular apparatus ... and disease of the peripheral motoric neurons." (Mylan(GAL) 05984) (emphasis added). M. Bretagne, et al., "Essais Cliniques en Anesthesiologie d'un Nouvel Anticholinesterasique la Galanthamine," Anesthesie Analgesie Reanimation, 1: 285-92 (1971) (cited at Levey ¶ 83, translation at JAN RAZ 0134055-61) notes that, as a cholinesterase inhibitor, "the activity of Galanthamine is relatively weak compared with that of neostigmine and [physostigmine]" and the authors suggest that its quick action in reversing curare paralysis may be due to the fact that "Galanthamine directly excites smooth muscle and striated muscle." (JAN RAZ 0134058). While we now know that galantamine in fact has an allosteric modulatory effect on the nicotinic receptor, this was unknown at the time, and these statements would instead have suggested that galantamine's principal action was peripheral, a highly undesirable feature for treatment of AD.

38. Not only was galantamine recognized as being a weaker cholinesterase inhibitor, its duration of action would not have been viewed in 1986 as meaningfully longer than

physostigmine or tacrine for purposes of treating a steadily progressive dementia such as AD. The pharmacokinetics of galantamine, particularly orally administered galantamine, does not appear to have been systematically studied before January 1986. What was published does not suggest that galantamine's half-life was particularly long. Bretagne, et al. (1971) states that at equivalently effective doses, "[g]alanthamine is faster in onset and **more transient in duration than that of neostigmine**." Bretagne et al., "Essais Cliniques en Anesthesiologie D'un Nouvel Anticholinesterasique la Galanthamine," Anesthesie Analgesie Reanimation, 1: 285-92 (1971) (JAN RAZ 0134057 (emphasis added)). For duration, they report simply that "the action of this product [galantamine] persists for over two hours." (JAN RAZ 0134061).

39. Yet, with regard to physotigmine's duration of action, R.C. Mohs et al. (1985) had similarly reported that "studies of orally administered physostigmine in patients with ataxia suggest that steady-state levels can be achieved with dosing every 2 hours." R.C. Mohs et al., "Oral Physostigmine Treatment of Patients With Alzheimer's Disease," Am. J. Psychiat. 142: 28-33 (1985), at p. 28. Similarly, Thal et al. (1983), had observed that "the biologically effective half-life of orally administered physostigmine is undoubtedly much longer than previously suspected." L.J. Thal et al., "Oral Physostigmine and Lecithin Improve Memory in Alzheimer's Disease," Ann. Neurol. 13: 491-96 (1983), at p. 495.

40. The articles Drs. Domino and Levey cite for the proposition that galantamine was longer acting than physostigmine arise in the context of conditions, such as scopolamine-induced amnesia, which are temporary in nature and involve acute rather than chronic administration of therapy. The pharmacologic considerations for such treatments are very different than those for treatment of AD. Suggestions that galantamine is a longer-acting or appropriate substitute for physostigmine in the context of such temporary or acute conditions would not lead one of

ordinary skill to conclude the galantamine was also a sufficiently long acting or appropriate substitute for physostigmine in the very different context of Alzheimer's Disease.

41. I believe that a person of ordinary skill, reviewing the relevant literature available in 1986, would not have concluded that galantamine's duration of action was sufficiently long to overcome any perceived deficiencies in physostigmine's duration of action – especially when combined with galantamine's significant perceived disadvantage, its weaker cholinesterase inhibitory effect.

42. In fact, Dr. Domino himself reached this conclusion in an article that he published in 1988. E.F. Domino, "Galanthamine: Another Look at an Old Cholinesterase Inhibitor," in Giacobini, E., and Becker, R., eds., Current Research in Alzheimer Therapy, pp. 295-303 (1988). In this article, Dr. Domino reviewed the pharmacokinetics of galantamine for purposes of evaluating the drug's potential for use in treating AD and concluded that galantamine was "**not a very long acting compound**" and was "**only as long acting as physostigmine but much less potent.**" (p. 301 (emphasis added)).

43. As a final note, none of the physostigmine or tacrine references cited by Dr. Levey or Dr. Domino actually suggest modifying the existing cholinesterase inhibitor approach by using galantamine. The references express the view that the efficacy of physostigmine and tacrine was limited, but did not propose that new cholinesterase inhibitors should be attempted. (The prevailing view was that if improvements were to be made, such improvements likely would come through efforts to develop entirely new cholinergic drugs.) For example, R. Mohs, et al. (1981) stated expressly that "no safe long-acting cholinesterase inhibitor is available at the present time." R. Mohs, et al., "Studies of Cholinergic Drug Effects on Cognition in Normal Subjects and Patients with Alzheimer's Disease," Aging 17: 225-30 (1981), at p. 226-227. And

B.S. Greenwald, et al. (1983) similarly warned that "currently available cholinergic agents are unable to substantially influence symptoms of AD." B.S. Greenwald, et al., "Neurotransmitter Deficits in Alzheimer's Disease: Criteria for Significance," J. Amer. Geriatrics Soc., 31(5): 310-16 (1983), at p. 313. These are articles from some of the leading figures in Alzheimer's research, and I do not believe that a person of "ordinary" skill would have ignored these express warnings in the very articles Drs. Domino and Levey cite on physostigmine in order to arrive at the conclusion that the old, weak cholinesterase inhibitor galantamine was a promising or even suitable substitute for physostigmine in treating AD. To the contrary, these statements would have instead further discouraged a person of ordinary skill from modifying those references to use galantamine in lieu of physostigmine or tacrine.

**C. Reasonable Expectation of Success**

44. The foregoing makes it clear to me that a person of ordinary skill in the art in January 1986 would have not had a reasonable expectation of success in using galantamine to treat Alzheimer's disease, even if such possible therapeutic use had occurred to him or her. The results of the studies on physostigmine did not establish proof of concept that cholinesterase inhibitors would work in treating Alzheimer's Disease; the outcomes of those trials were equivocal and inconsistent. If anything, the clinical trial results of physostigmine would have led a person of ordinary skill to conclude that galantamine would have an even lesser chance of success, because it is "only as long acting as physostigmine but much less potent." E.F. Domino, "Galanthamine: Another Look at an Old Cholinesterase Inhibitor," in Giacobini, E., and Becker, R., eds., Current Research in Alzheimer Therapy, pp. 295-303 (1988), at p. 301. And of course, physostigmine had not succeeded.

45. My opening report further supports the fact that a person of ordinary skill would not have had a reasonable expectation that galantamine would successfully treat Alzheimer's

disease. That researchers were skeptical of a cholinesterase inhibitor approach to the treatment of Alzheimer's disease cuts directly against a reasonable expectation of success for galantamine.

## VI. ENABLEMENT

46. Dr. Levey's report also claims that the '318 patent does not "enable" the patented invention because the patent does not disclose sufficient information to show that galantamine would be a therapeutically effective treatment for Alzheimer's disease. (Levey ¶ 120). I disagree. Dr. Davis's patent discloses sufficient information such that a person of ordinary skill could make or use her invention.

47. In particular, the patent tells a researcher what steps that he or she should take in order to implement Dr. Davis's invention. The patent describes the animal testing needed to confirm the efficacy of galantamine in the treatment of Alzheimer's disease:

> The following test provides a good animal model for Alzheimer's disease in humans: A selective lesion is placed in a subcortical nucleus (nucleus basalis of Meynert) with a resultant cortical cholinergic dficiency, similar in magnitude to that seen in early to moderate stage Alzheimer's disease. . . . Drugs that can normalize these abnormalities would have a reasonable expectation of efficacy in Alzheimers' disease. ('318 patent, p. 2, column 2, ll. 45-54).

48. Based on my experience in drug development, I agree that these animal tests would be the logical next step, in 1986, to confirm the utility of galantamine to treat Alzheimer's disease. The patent thus describes for a person of ordinary skill how to best confirm – short of conduct human trials – the therapeutic activity of galantamine described in the patent.

49. Both Drs. Domino and Levey further assert that claim 4 of the patent is not enabled because there is "no support for any dosage of galantamine at the high end of her range." (Levey ¶ 121; see also Domino ¶ 97). But a person of ordinary skill reading the '318 patent would have been aware of how to arrive at the correct dosage of galantamine. That is, he or she would have titrated the dose – a standard clinical practice in which a patient is started

conservatively with a low dosage, which is then slowly increased to arrive at a therapeutically effective dosage range. The patent itself refers to this technique. (See '318 patent, col. 1, lns. 64-66) ("It may be necessary to begin at lower doses than are ultimately effective."). In my opinion, the patent provides sufficient information to enable a person of ordinary skill to determine an appropriate dose range for galantamine.

## VII. MISCELLANEOUS

50. Finally, I note that both Dr. Levey and Dr. Domino criticize the way that the '318 patent was prosecuted in the Patent Office. I do not understand that the manner in which a patent is prosecuted to be relevant to the questions of anticipation, obviousness, and enablement that the defendants are raising in this case. I am also not an expert in patent prosecution. However, based on my review of the patent prosecution from the standpoint of an expert in drug discovery and development in the Alzheimer's field, I do not agree with Dr. Levey's or Dr. Domino's criticisms. In my opinion, the statements made to the Patent Office were scientifically fair and reasonable.

51. For example, both Dr. Levey and Dr. Domino criticize Dr. Bonnie Davis for failing to cite the Bhasker article to the Patent Office. (Levey ¶ 125; Domino ¶ 63). I find this criticism absurd. As I discussed above, a reasonable scientist would not have read the Bhasker article as having anything to do with Alzheimer's disease; it is Dr. Levey's and Dr. Domino's purported reading of the Bhasker article that is unreasonable.

52. In addition, I understand from Dr. Bonnie Davis's deposition that she was not even aware of the Bhasker article at the time she obtained the patent. I find this too entirely reasonable. Again, as discussed above, the Bhasker article had never been indexed or cited at the time the patent was prosecuted, and was published in an obscure journal, The Antiseptic, that no one researching Alzheimer's disease at the time would have thought to review in the course of

his or her research. I am not aware that either Dr. Levey or Dr. Domino ever cited the Bhasker article in any of their publications on Alzheimer's disease – why then would they expect Dr. Bonnie Davis to have done so?

53. Second, both Dr. Levey and Dr. Domino take Dr. Bonnie Davis to task for purportedly failing to inform the Patent Office of the cholinergic hypothesis of Alzheimer's Disease. Dr. Domino asserts, for example, that "she completely ignores the cholinergic hypothesis of Alzheimer's disease" and fails to discuss the physotigmine work conducted by Dr. Ken Davis and others. (Domino ¶ 59; see also Levey ¶ 126). But this assertion is plainly contradicted by the patent itself and by the document entitled "Amendment Responsive to Office Action of April 10, 1986," which I understand was submitted to the Patent Office in connection with prosecuting the '318 patent in September 1986.

54. First, in column 2 of her patent, Dr. Bonnie Davis expressly references the "central cholinergic deficiency" in mild to moderate Alzheimer's disease in proposing a "good animal model" for the disease. The patent states:

> The following test provides a good animal model for Alzheimer's disease in humans: A selective lesion is placed in a subcortical nucleus (nucleus basalis of Meynert) **with a resultant cortical cholinergic deficiency, similar in magnitude to that seen in early to moderate stage Alzheimer's disease**. ('318 patent, col. 2, lns. 45-50 (emphasis added))

The patent thus clearly mentions the cholinergic deficiency associated with Alzheimer's disease and does so in the context of proposing an animal model for evaluating pharmacologic treatments.

55. In addition, Dr. Bonnie Davis' September 1986 submission to the Patent Office provided further materials concerning the cholinergic hypothesis and its therapeutic implications. That document cites (on page 2) two review articles about Alzheimer's disease – one by

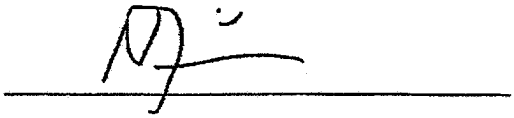
Hershenson & Moos and the other by Kendall – and I understand that copies of both those articles were submitted to the Patent Office with the document. Both those article discuss the cholinergic hypothesis, its potential utility in developing treatments for AD, and the work done on cholinesterase inhibitors (among other compounds) in connection with that hypothesis.

56. In addition, the same paragraph of Dr. Bonnie Davis' submission to the Patent Office also describes the physostigmine work, explaining that "although useful results have been reported in some cases by treatment with physostigmine, its poor therapeutic index is likely to preclude its widespread use and there is no generally effective treatment available." This description is entirely fair and, indeed, if anything more favorable than many of the judgments about physostigmine reviewed above. In fact, her judgment has been borne out by the passage of events, as physostigmine was never approved by FDA for treatment of AD (despite considerable effort by Forest Laboratories) and has never achieved widespread use for treatment of that disease.

57. Finally, Dr. Domino takes issue with Dr. Bonnie Davis' analogy to treatment of diabetes in her submission to the patent office, suggesting that the "proper analogy for galantamine ... would have been for Dr. Davis to compare the effect of insulin in normal adults to the effect of insulin in diabetes." (Domino ¶ 58). But it is Dr. Domino's analogy which is incorrect. Diabetes is characterized by a degradation of the body's ability to produce insulin; treatment by insulin thus replaces the missing biological agent. The analogy to insulin in the AD context would be acetylcholine precursor therapy – also intended to replace the missing biologic agent (in AD, acetylcholine). Precursor therapy failed in the treatment of Alzheimer's disease, and this failure, as I explained in my opening report, only furthered the skepticism of a cholinergic approach to treatment of AD. I find nothing misleading about Dr. Bonnie Davis'

analogy, but it is certainly worth noting that even Dr. Domino's suggested alternative (that is, administration of the missing biologic agent) supports the validity of the '318 patent, since such administration (of acetylcholine precursors) did not work.

Date: September 11, 2006



# EXHIBIT A

Documents

1. United Kingdom Patent No. 942,200
2. United States Patent No. 4,663,318
3. Letter from Frantsits and Mucke to Bonnie Davis re: galanthamine patents [SYN RAZ 0000181]
4. Letter from Bonnie Davis to Alfred Gagne re: support for claim of galanthamine's superiority in treatment of Alzheimer's disease [SYN RAZ 0017587]
5. Letter from Bonnie Davis to Dr. William Cressman re: enclosed "new set of materials on the use of galanthamine for Alzheimer's disease" [SYN RAZ 0000761 -763]
6. Shire complaint filed in Vienna Commercial Court [SYN RAZ-0018366 - 18374]]
7. Amendment [of patent application] responsive to office action of April 10 [JAN RAZ-0000031-0000039]
8. Physician's Desk Reference (2006)
9. Deposition transcript of Dr. Bonnie Davis (February 8-9, 2006) and Exhibits

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# EXHIBIT M

**UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF DELAWARE**

| | |
|---|---|
| IN RE: '318 PATENT INFRINGEMENT LITIGATION | Civil Action No. 05-356-KAJ (Consolidated) |

**SECOND EXPERT REPORT OF DR. MURRAY A. RASKIND**

## I. INTRODUCTION

1. This report supplements my opening expert report of July 28, 2006. I have been asked to review the claims made by Dr. Edward Domino and Dr. Allan Levey that U.S. Patent No. 4,663,318 ("the '318 patent") is invalid due to anticipation, obviousness, or lack of enablement. This report sets forth my opinions concerning the validity of the '318 patent.

2. In forming the opinions described in this report, I have reviewed the reports of Dr. Domino and Dr. Levey, the documents discussed in those reports, the materials referenced in my opening report and in Attachment A to this report. I have also relied upon my more than 30 years experience as a clinician and researcher in Alzheimer's disease and knowledge of the relevant literature and state of the art in forming my opinion.

3. In summary, it is my opinion that the '318 patent is not invalid due to anticipation. The central reference relied upon by the defendants' experts -- P.A. Bhasker, "Medical Management of Dementia," The Antiseptic, 71:45-47 (1974) (the "Bhasker article") -- does not in any way describe the use of galantamine for the treatment of Alzheimer's disease. In fact, no literature as of 1986 described or even suggested galantamine to treat Alzheimer's

disease. Furthermore, the Bhasker article would not have been accessible using standard reference search techniques of those skilled in the art.

4. It is also my opinion that the '318 patent is not invalid as obvious given the state of the art as of 1986. Neither the references relied upon by Dr. Levey and Dr. Domino nor any other publications in the field at that time suggest in any way the use of galantamine for the treatment of Alzheimer's disease.

5. It is further my opinion that Dr. Davis' '318 Patent would enable one of ordinary skill in the art to practice the claimed invention. The '318 patent outlines an approach for Alzheimer's disease researchers to confirm the efficacy and tolerability of the invention and describes the appropriate dose titration (beginning with a low dose and increasing the dose until a therapeutic response is noted or drug intolerance intervenes) to enable one skilled in the art to treat an Alzheimer's patient with galantamine.

## II. A PERSON OF ORDINARY SKILL IN THE ART

6. A person of ordinary skill in the art in treating Alzheimer's disease in 1986 would have been a medical doctor treating elderly patients, that is, a physician likely to have responsibility for the care of patients suffering from Alzheimer's disease.

7. I disagree with Dr. Levey's and Dr. Domino's description of the level of ordinary skill in the art to the extent they assert a person of ordinary skill would be "a M.D. or Ph.D. interested in the field of Alzheimer's disease research" (Levey ¶ 19) actually engaged in Alzheimer's research. I believe their description exaggerates the level of skill of the ordinary person. In 1986, the majority of doctors treating Alzheimer's patients had been taught little about the disease in medical school, and very few had any training or experience in the field of

Alzheimer's research. Thus, the level of "ordinary" skill in the field of treating Alzheimer's patients would have come from being a doctor encountering and caring for patients with the disease.

8. However, the level of skill that was ordinary in 1986 does not affect my opinions concerning the validity the '318 patent. Even under the definition given by Dr. Domino and Dr. Levey of the person of ordinary skill in the art, it would remain my opinion that the '318 patent is not invalid for reasons of anticipation, obviousness, or lack of enablement.

## III. ANTICIPATION

9. I have been informed that the statutory requirement for anticipation of a patent claim is that the claimed invention must be shown to be "known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent." 35 U.S.C. § 102(a). In order for that article to anticipate claims 1 and 4 of the '318 patent, I understand that this article must describe the invention claimed in those patent claims. That is, the article must describe, to one of ordinary skill in the art, each and every element of those claims.

10. I have been informed that the statutory requirement for anticipation of a patent also requires the invention to be patented or described "in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States." 35 U.S.C. § 102(b). For the article to qualify as a "printed publication," I understand that the Bhasker article must be "publicly accessible." That is, it must be accessible to persons skilled or interested in the art. I understand that indexing of

the article is relevant to determining whether it was accessible to persons skilled or interested in the art.

11. Defendants' experts have asserted that the Bhasker article anticipated the '318 patent. They are incorrect. A person of ordinary skill would not interpret the Bhasker article in 1986 to suggest that Bhasker describes galantamine as a treatment for Alzheimer's disease.

12. Bhasker's only reference to galantamine is in a context clearly unrelated to Alzheimer's disease. Specifically, galantamine is discussed as a "deinhibitory" treatment for "local brain damage." (p. 46). Bhasker states that the Russian neuroscientist Dr. Luria and his colleagues "have suggested measures of improving the higher functions in cases of local brain damage like tumour, head injury, infarct [stroke] etc., by deinhibitory procedures and re-education of the rest of the brain." They go on to quote Dr. Luria as defining "deinhibition" as "facilitation of acetylcholine activity by small daily doses of cholinesterase inhibitors (Neostigmine, Gallanthamine etc.)." (p. 46).

13. Alzheimer's disease is not a type of local brain damage. It is not analogous to "tumour, head injury, or infarct." It is also noteworthy that this concept of "deinhibition" as described by Dr. Luria is not and never has been an approved or recognized treatment for local brain injury or any other neurologic disorder in Western medicine.

14. Alzheimer's disease is never mentioned by Bhasker. He does not even use the term "Senile Dementia" that prior to 1970 was often used (albeit incorrectly) to denote late onset Alzheimer's disease. Nonetheless, Dr. Levey and Dr. Domino assert that the Bhasker article's reference to "progressive dementia" would be understood to encompass Alzheimer's disease. (Levey ¶ 99; Domino ¶ 79). They assert that one of ordinary skill would understand that the Bhasker description of "irreversible cases belong[ing] to the category of dementias where there

is a progressive fall-out of neurons and the course of the illness is rapidly downhill" encompasses Alzheimer's disease. (p. 45). I disagree.

15. It is well known that the onset of Alzheimer's disease progresses gradually over an average 8-10 years and as long as 15 years. In fact, the early stage of Alzheimer's disease progresses so slowly that the emergence of the clinical picture is classically considered "insidious." The 1984 Merck Manual, cited by Dr. Domino (Domino ¶ 79) and Dr. Levey (Levey ¶ 99), states that "the most common clinical picture is of slow disintegration of personality and intellect." Berkow R, *Dementia. Merck Manual of Diagnosis and Therapy*, (14th ed. 1982), at 1305 (emphasis added). Additionally, Rathman and Conner, also cited by Dr. Levey (Levey ¶¶ 78, 102-103) and Dr. Domino (Domino ¶ 86), note "[t]he onset generally is insidious occurring over several years." Rathman and Conner, "Alzheimer's Disease, Clinical Features, Pathogenesis, and Treatment," Drug Intelligence and Clinical Pharmacy, 18: 684-691, 684 (1984). Thus, a person of ordinary skill would not view the course of an Alzheimer's patient as proceeding "rapidly downhill."

16. Nor does the Bhasker article suggest galantamine as a treatment for "progressive dementia." In fact, the article reaches the opposite conclusion. It expressly states that progressive dementias are untreatable. Bhasker concedes that "[w]ith regard to progressive dementia, there appears very little to offer. Only management and no treatment is possible." (p. 45)(emphasis added). Management generally refers to environmental and behavioral approaches that reduce distress -- not treatment of the disease.

17. The fact that Bhasker lumps neostigmine with galantamine as an agent for "deinhibition" further indicates that Bhasker is not describing galantamine as a therapy for Alzheimer's disease. Neostigmine cannot penetrate the blood brain barrier and would not have

access to the brain following oral or even intravenous administration. Therefore, neostigmine would be a totally illogical treatment for a brain disease such as Alzheimer's disease.

18. The Bhasker article would not have taught a person of ordinary skill interested in either Alzheimer's disease or galantamine in 1986 because it was inaccessible using any standard search or index technique available at the time. Specifically, in 1986, the Index Medicus, which was the only widely used source of cited medical literature, did not contain articles appearing in the Indian journal The Antiseptic in which the Bhasker article was published.

## IV. NON-OBVIOUSNESS

19. I have been informed that the following factors are relevant in determining whether a patent is invalid for reasons of obviousness: (1) the scope and content of the prior art; (2) the differences between the patented invention and the prior art; (3) the level of ordinary skill in the art; and (4) objective considerations of non-obviousness. I addressed objective considerations of non-obviousness in my opening report. In forming my opinion, I have also been asked to consider whether the prior art would have provided a person of ordinary skill a motivation to combine or modify the prior art references so as to arrive at the claimed invention and also whether it would have provided such a person with a reasonable expectation of success in doing so.

20. Dr. Domino and Dr. Levey contend the '318 patent was obvious in light of the prior art, primarily relying upon select physostigmine clinical trials which they claim demonstrate that galantamine would have been obvious as an effective treatment for Alzheimer's disease. They are incorrect.

A. Prior Art - Physostigmine and Tacrine Clinical Trials

21. Physostigmine clinical trials did not "clearly show[] that the drug was effective in treating dementia symptoms associated with Alzheimer's disease" as Dr. Levey declares. (Levey ¶¶ 36, 113). In fact, physostigmine had not and still has not been demonstrated to be clinically effective. The results of the clinical studies on physostigmine as of 1986 were equivocal at best and their conclusions controversial in the field. Articles cited by Dr. Levey and Dr. Domino confirm this.

22. Mohs et al., "Oral Physostigmine Treatment of Patients with Alzheimer's Disease," Amer. J. Psychiatry, 142(1):28-33 (1985), cited by Dr. Levey (Levey ¶ 76), studied oral physostigmine in 12 Alzheimer's patients. The authors do not describe physostigmine as therapeutically effective. Instead, they conclude that the results could be interpreted from a clinical perspective either to demonstrate that "physostigmine, in the doses used in this study, does not have therapeutic benefits comparable to those seen with L-dopa in Parkinson's disease or with neuroleptics in schizophrenia" because it produced "a consistent and clinically evident improvement in symptoms for only about 30% of patients." (p. 31). The authors call for large clinical trials to identify individuals likely to benefit from oral physostigmine. (p. 32).

23. In "Clinical Studies of the Cholinergic Deficit in Alzheimer's Disease," J Amer Geriatrics Soc., 33:749-57 (1985) cited by Dr. Levey (Levey ¶ 83) and Dr. Domino (Domino ¶ 41), Mohs et al. studied the acute effects of intravenous and oral physostigmine. They found that intravenous physostigmine modestly enhanced memory in most patients, but they were unable to correlate improvement with any "clinical variable." (p. 755). Oral physostigmine (the root of administration that would be necessary in clinical practice) slightly improved memory in roughly half of the patients. The authors acknowledge that "the search for any reasonably effective

pharmacologic treatment must address several different problems if it is to succeed" but warned about difficulties in diagnosis, the presence of neurochemical deficits other than acetylcholine in Alzheimer's patients, and the difficultly in determining whether a cholinomimetic drug is in fact improving a patient's cholinergic activity. (p. 755). However, the authors note that even when these conditions are met, "the use of such drugs could be severely limited" due to cholinergic cells having relatively few postsynaptic nonoverlapping projections. (p. 756)(emphasis added). Therefore, it would be difficult for surviving cholinergic cells to compensate functionally for lost cholinergic neurons by increasing their firing rate. Furthermore, none of these drugs (cholinesterase inhibitors) may be able to duplicate the phasic action of cholinergic cells in transmitting information.

24. K. Davis and Mohs, "Enhancement of Memory Processes in Alzheimer's Disease with Multiple-Dose Intravenous Physostigmine," Am. J. Psychiat., 139(11): 1421-24 (1982), similarly recognized the clinical limitations of their work. The authors administered physostigmine intravenously to Alzheimer's patients. While low doses of intravenous physostigmine transiently improved the ability of patients with Alzheimer's disease to store information into long-term memory, the authors caution that "until there is long-term administration of cholinomimetic agents to patients with Alzheimer's disease, it will be impossible to judge their ultimate clinical utility." (p. 1423)(emphasis added).

25. B.S. Greenwald, et al., "Neurotransmitter Deficits in Alzheimer's Disease: Criteria for Significance," J. Amer. Geriatrics Soc., 31(5):310-16 (1983), cited by Dr. Levey (Levey ¶ 32), acknowledge that the clinical utility of cholinomimetics like physostigmine had not been demonstrated. The authors reviewed pharmacologic enhancement of the cholinergic system in light of the insight learned from Parkinson's disease, a disease that reflects a deficiency of

dopamine. They declare that "positive effects of cholinomimetics have been reported; however, a level of clinical utility has not been achieved." (p. 313)(emphasis added). One explanation they offer in their attempt to account for the differential effect of dopamine and acetylcholine agonists is that "currently available cholinergic agents are unable to substantially influence symptoms of AD." (p. 313)(emphasis added).

26. In "Cholinergic Modulation of Memory in Rats, Psychopharmacology (Berlin), 87(3):266-71 (1983), cited by Dr. Levey (Levey ¶ 32), V. Haroutunian et al. reported that both the anticholinesterase agents including physostigmine and the post-synaptic cholinergic agonists agents arecoline and oxotremorine enhanced retention of learned responses in rats at low doses and impeded retention at high doses. The article notes that prior studies found the effects the drugs in this study to be conflicting "with some authors finding potentiation of learning and memory, others reporting disruption of memory processes, and still others finding no significant effects." (p. 269). The authors' sole reference to treatment of Alzheimer's disease is their speculation that "[i]f this generalization [about similar effects in man] should prove valid in experiments with normal human subjects, it may be possible to use these or similar cholinergic compounds in the treatment of memory disorders such as those characteristic of Alzheimer's disease." (p. 270). However, the article's suggestion that cholinergic agents may impede retention at higher doses would discourage its clinical use. None of the compounds is described as therapeutically effective in Alzheimer's patients.

27. C. Johns, et al., "The Cholinergic Treatment Strategy in Aging and Senile Dementia," Psychopharmacology Bulletin, 19(2):185-97 (1983), cited by Dr. Domino (Domino ¶ 85), reviewed studies of the cholinesterase inhibitors physostigmine and tacrine in Alzheimer's patients. The authors note that the "only currently available relatively safe pharmacologic agents

of this type are physostigmine, which produces chronic enhancement of the cholinergic system by competitively inhibiting acetylcholinesterase, and tetrahydroaminoacridine (THA)[tacrine], a centrally-acting reversible acetylcholinesterase inhibitor with a longer half-life than physostigmine." (p. 189). They acknowledge that the variability of physostigmine test results, both in terms of overall efficacy and specific areas of improvement, has generated debate over the clinical utility of cholinesterase inhibitor therapies." (p. 189). Furthermore, they noted that the practical clinical utility of the drugs remains uncertain. (pp. 191-92).

28. Johns and her colleagues cast doubt on the efficacy of cholinesterase inhibitors like physostigmine and tacrine in treating Alzheimer's disease. They conclude that those drugs "share a fundamental limitation in that they are dependent on an intact presynaptic neuron to provide a substrate for their activity." (p. 192). Instead, the authors point to postsynaptic muscarinic agonist like oxotremorine as "a more ideal compound." (p. 192). Finally, the authors expressly reject Dr. Levey's and Dr. Domino's claim that clinical utility has been demonstrated for any cholinergic approach. They declare that "[t]he success of cholinomimetic treatment strategies thus far has been modest, and definitive treatment of SDAT [senile dementia of the Alzheimer's type] awaits clarification of complex neurochemical variables, delineation of parameters that can predict response, and development of appropriate safe, long-acting pharmacologic agents." (p. 193).

29. The articles Dr. Levey and Dr. Domino rely on simply do not demonstrate that physostigmine or tacrine were therapeutically effective for the treatment of Alzheimer's disease as of 1986. Even the laundry list of articles cited in Dr. Levey's report (Levey ¶ 83), without explanation, demonstrate limited, inconclusive, and at times, negative results of physostigmine studies. Levy, et al., "Research Subject Recruitment for Gerontological Studies of

Pharmacological Agents," Neurobiology of Aging, 3(1): 77-79 (1982)(noting potential problems with recruitment, sample size, and diagnosis can raise issues with interpretation of Alzheimer's disease study results); Smith and Swash, "Physostigmine in Alzheimer's Disease," The Lancet, 1:42 (1979)(reporting that physostigmine appeared to improve name recall but none of the other memory tests); Peters, et al., "Effects of Physostigmine and Lecithin on Memory in Alzheimer's Disease," Annals of Neurology, 6(3): 219-21 (1979)(finding neither physostigmine nor lecithin alone consistently improved long-term memory processes and noting that physostigmine and lecithin had no obvious effect on general cognitive efficiency or social functioning during the brief course of the study); K. Davis, et al., "Physostigmine: Improvement of Long-Term Memory Process in Normal Humans," Science, 201(4352):272-74 (1978) (noting considerable variability between subjects in their physostigmine study).

30. In fact, many studies known to those skilled in the art failed to demonstrate any positive effect of physostigmine and tacrine on symptoms of Alzheimer's disease. Jotkowitz, "Lack of Clinical Efficacy of Chronic Oral Physostigmine in Alzheimer's Disease" Ann. Neurol., 14:690-691, 691 (1983)(finding "no improvement" from physostigmine and declaring "the present study confirms the previous report of the lack of benefit of physostigmine in AD and extends the observation to long-term oral administration.")(emphasis added); Kaye, et al., "Modest Facilitation of Memory in Dementia with Combined Lecithin and Anticholinesterase Treatment," Biol. Psychiatry, 17:275-90 (1982)(finding no overall effect of tacrine alone on cognitive function in patients with Alzheimer's disease); Drachman, et al. "Memory Decline in the Aged: Treatment with Lecithin and Physostigmine," Neurology, 32:944-50, 949 (1982)(declaring that "physostigmine failed to improve performance on memory tasks" in healthy elderly subjects selected because they were believed to show a decline in memory and

cognition and more sensitivity to cholinergic manipulation); Wettstein, et al., "No Effect from Double-Blind Trial of Physostigmine and Lecithin in Alzheimer's Disease," Ann Neuro 12:210-212, 211 (1983)(concluding "[n]o improvement in recent memory or other psychological functions could be demonstrated [with physostigmine]."); Sullivan, et al. "Physostigmine and Lecithin in Alzheimer's Disease," Aging, 19: 361-67, 362 (1982)(finding that "physostigmine infusion did not produce any reliable change in the performance of these patients as a unitary group."); Caltagirone, et al., "Oral Administration of Chronic Physostigmine Does Not Improve Cognitive or Mnestic Performances in Alzheimer's Presenile Dementia," Intern J. Neuroscience, 16:247-249, 248 (1982)(concluding "no difference was found for the results obtained on MDB[Mental Deterioration Battery] by AD patients before and after treatment [of physostigmine]."); Ashford, et al., "Physostigmine and its Effect on Six Patients," Am J Psychiatry, 138(6):829-30, 830 (1981) (finding that physostigmine "did not improve learning or memory ... in older patients who were moderately to severely demented" and noting a "trend toward poorer verbal retention and less improvement on trials after patients had received physostigmine on the Buschke wordlist learning test" and "[a] similar trend toward poorer visual retention on the Benton visual retention test was noted after physostigmine."); Delwaide, et al., "Acute Effect of Drugs upon Memory of Patients with Senile Dementia," Acta Psychiat. Belg., 80:748-54 (1980)(finding physostigmine produces no improvement on memory but noting in contrast that the hormonal treatment lysine-vasopressin and the nootropic piracetam did improve memory).

31. Nor did those skilled in the art reviewing these clinical trials find that they stood for the proposition that "the ideal drug candidate for treating Alzheimer's disease would perform like physostigmine." (Levey ¶ 36). Raymond Bartus and his coauthors in 1986 reviewed the

physostigmine literature and found that "[a]lthough positive effects have been obtained in both aged humans and nonhuman primates with memory impairments, the effects are quite subtle and require strictly controlled test conditions and special attention to large individual variations in the most effective dose." Bartus et al., "Cholinergic Treatment for Age-Related Memory Disturbances: Dead or Barely Coming of Age?" in Crook, T., et al., eds., *Treatment Development Strategies for Alzheimer's Disease* 421-450 (1986), at 428. Nonetheless they found that "[w]hatever the positive results that have been claimed or obtained with cholinergic agents, one must recognize that they are extremely subtle, quite variable, and offer little or no significant therapeutic relief in activities of daily living." (p. 428)(emphasis added). In fact, the article declares that that "we are probably a long way from achieving an effective treatment for the symptomatic loss of cognitive function in senescent or demented patients." (p. 441). See also Bartus et al., "Cholinergic Hypothesis: Its History and Future," in Olton, et al., eds., *Memory Dysfunctions: An Integration of Animal and Human Research from Preclinical and Clinical Perspectives* (Annals of the New York Academy of Sciences), 444:332-58 (May 30, 1985).

32. Bartus was not alone in his opinion. Kaye Rathmann and Christopher Conner, which Dr. Levey and Dr. Domino themselves cite, wrote in 1984 that "[d]espite encouraging results with physostigmine, the clinical importance and usefulness of this class of agents remain undetermined." K. Rathmann and C. Conner, "Alzheimer's Disease Clinical Features, Pathogenesis, and Treatment," Drug Intelligence and Clinical Pharmacy, 18:684-91, 689 (1984). The authors review a number of studies involving physostigmine and conclude: "[c]learly, controlled studies evaluating long-term treatment are required to determine the clinical usefulness of acetylcholinesterase inhibitors in Alzheimer's disease ...." (p. 688). Furthermore,

Dr. Berg, a pioneer neurologist in academic Alzheimer's disease research, noted in 1984 that "there have been inconsistencies in the findings from various laboratories in experiments testing the cholinergic hypothesis. Responses of patients with AD to cholinomimetic drugs and other agents to promote cholinergic transmitter function have been spotty and disappointing." Berg, "Aging and Dementia," in *Neurological Pathophysiology* 250-273 (1984), at 270.

33. Even when small and transient improvements occurred in one or a few cognitive tasks after single-dose physostigmine administration, such results were inadequate for inferring clinical efficacy. These acute, short term trials could not by the nature of their design demonstrate clinically efficacy. Any improvements found in such tests are not sufficient to constitute clinically meaningful improvements. Smaller improvements in cognitive test scores do not constitute effective therapy -- the therapy must result in clinical benefits.

34. The FDA emphasized this in its 1990 Guidelines for the Clinical Evaluation of Antidementia Drugs. Leber, "Guidelines for the Clinical Evaluation of Antidementia Drugs: First Draft" (Nov. 8, 1990). To be approved as a treatment for Alzheimer's disease, a drug must establish that it "has a clinically meaningful effect" and "exerts its effect on the 'core' manifestations of dementia"; that is, on a global assessment performed by a skilled clinician. (Guidelines at 4.4.2). The requirement of improvement on a global assessment scale precluded the approval of drug products that "produce no clinically meaningful effects on the overall status (e.g., health, function, etc.) of demented patients, but do because of their pharmacologic activity, cause the detectable changes in patient performance on objective tests that are of uncertain clinical relevance." (Guidelines at 4.4.2.). Clinical studies on physostigmine and tacrine as of 1986 did not even approach establishing the sort of reliable, clinically meaningful improvements in Alzheimer's patients that constitute a treatment.

35. The comments at the FDA's 1989 Antidementia Drug Assessment Symposium, approximately three years after Dr. Bonnie Davis' invention made this clear. As mentioned in my opening report, I was a participant of that symposium. There many of the leading clinical investigators in the field of Alzheimer's disease (including many of the authors whose works are cited by Dr. Domino and Dr. Levey) discussed and debated the challenges of finding a treatment for Alzheimer's disease, including the obstacles to obtaining reliable, clinically meaningful results addressing the global improvement of the disease.

36. Dr. Leber, Director of the FDA's Division of Neuropharmacological Drug Products, stated the purpose of the forum was for "open and free exchange of information and ideas among acknowledged experts about the development, testing, and assessment of drug products that might be classified as antidementia agents." (FDA Antidementia Drug Assessment Symposium Transcript 19:9-13). He recognized the very discouraging efforts to date to find an effective treatment of any sort for Alzheimer's disease. As he noted, "at this point in time, even a safe and effective symptomatic treatment for some cardinal sign and symptom of Alzheimer's would constitute a substantive therapeutic advance." (10:2-5). In trying to explain the lack of success in finding a useful treatment to help Alzheimer's patients in any way, Thal decried "the lack of an approved antidementia drug" as "a reflection of the inadequacies of the drugs so-far tested, not of our assessment methodologies or imagined regulatory biases." (17:23-25)(emphasis added).

37. Dr. Drachman explained that the lack of approval was not simply due to heightened FDA regulations. "Our biggest problem" in finding a effective drug, according to Drachman, is not "that we can't nail down, using precise measures, the exact degree of efficacy

of powerful and effective drugs" but that "[w]e don't have any drugs that are really doing a hell of a lot. That is where I would start." (37:25-38:4).

38. I, myself, expressed frustrations I had with attempting to find an effective treatment for Alzheimer's disease. I noted that a recent study at our Alzheimer's disease research center failed to demonstrate that an antidepressant was superior to placebo for depression complicating Alzheimer's disease. These results surprised me and my colleagues for we believed based on open label clinical experience that antidepressants indeed appeared effective for depression in Alzheimer's patients. Our study convinced me that "no matter what aspect of Alzheimer's disease you wish to treat, a controlled trial is absolutely necessary." (65:9-11). I warned that "if you base your judgment of efficacy on large clinical experience after several years, all of these drugs will be effective. Everybody believes, especially if they have a convincing care provider, that whatever is being given to them is working somehow, at least the care providers do. And I think that is dangerous." (65: 11-14).

39. Dr. Thal similarly recognized the limitations of the studies conducted to date. "I think everyone has agreed that to definitively release a drug, one needs a controlled trial." (67:19-20).

40. Results of open clinical studies in and of themselves would not necessarily provide a treatment for Alzheimer's disease. As Dr. Thal explained, mere changes to test scores are in and of themselves insufficient to demonstrate clinically therapeutic and meaningful results:

> it has to be a clinically-observable effect by someone and that if you increase the point score of a dementia patient on any cognitive test that you show, but that neither a clinician nor a family member nor another member of society can discern that effect on that individual, then it is not worth releasing that drug. (111:23 -112:3).

41. The sentiments and concerns expressed by those experts in the field at the Antidementia Symposium in 1989 make it clear that the state of the art had not provided any sort of reliable, clinically meaningful improvements in Alzheimer's patients that would support the conclusion that any treatment, let alone cholinesterase inhibitors like physostigmine and tacrine, were therapeutically effective as a treatment for Alzheimer's disease.

42. No article referenced by Dr. Levey and Dr. Domino point to any drug being clinically effective. As of January 1986, no drug had been demonstrated clinically effective as a treatment for Alzheimer's disease.

B. Motivation to Combine

43. In 1986, a person of ordinary skill in the art would not have found that galantamine was a treatment for Alzheimer's disease. They would not have been motivated to combine the literature about physostigmine and tacrine in Alzheimer's disease with the literature about galantamine use for other conditions.

44. None of the literature cited by Dr. Domino or Dr. Levey describes galantamine as a possible treatment for any dementia including Alzheimer's disease. In fact, some of the prior art argues against the use of galantamine for dementia. The Pernov article describes principal application of Nivaline [galantamine] as treatment for "diseases of the neuromuscular apparatus ... and disease of the peripheral motoric neurons." K.G. Pernov, "Nivalin and its Curative Effect Upon Diseases of the Nervous System," Psychiatry and Neurology and Medical Psychology Bulletin on Research and Practice, 13(11) 416-420 (1961)(translation at Mylan(GAL) 05984, 05985). In Alzheimer's disease, central activity is required. Substantial peripheral effects would cast doubt on galantamine tolerability.

45. Nor would its possible use in reversing the central effects of scopolamine be persuasive. Dr. Levey and Dr. Domino rely on such articles by Baraka, et al., "Reversal of Central Anticholinergic Syndrome by Galanthamine," JAMA, 238:2293-2294 (1977) (Levey ¶¶ 77, 115; Domino ¶ 89), D.A. Cozanitis, "Galanthamine Hydrobromide, a Longer Acting Anticholinesterase Drug, in the Treatment of the Central Effects of Scopolamine (Hyoscine)," Anaetheist, 26, 649-650 (1977) (Levey ¶¶ 75, 103, 115-116), or D.A. Cozanitis, "L'hydrobromide de Galanthamine: Unsubstitute du Sulfate D'eserine (Physostigmine) pour le Traitement des Effects Cerebraux dex Substances Anti-Cholinergiques," Nouv. Presse Med., 7(45):4152 (1978)(Domino ¶ 88). This reliance is misplaced as none of those articles discusses Alzheimer's disease or dementia. Scopolamine induces a temporary delirium (reversible disruption of brain physiology) -- not a chronic and progressive dementia secondary to death of brain neurons. The fact that galantamine, like physostigmine and other cholinergic agents, had efficacy in reversing the central effects of scopolamine would not suggest to one of ordinary skill in the art that galantamine was a substitute for physostigmine in treating Alzheimer's patents.

46. In "Studies of Cholinergic Drug Effects on Cognition in Normal Subjects and Patients with Alzheimer's Disease," Aging, 17:225-230 (1981), cited by Dr. Domino (Domino ¶ 42), Mohs et al. criticize the scopolamine model as a guide to Alzheimer's research. The authors recognized that Alzheimer's disease does not involve a chemically-induced blockade of cholinergic receptors: "we know of no disease in which memory is impaired due to cholinergic blockade. Alzheimer's disease appears to affect primarily the presynaptic functions of cholinergic neurons and affects receptors only to a lesser extent." (p. 229).

47. Drs. Levey and Domino still claim that pharmacologic properties of galantamine made it an obvious substitute for physostigmine. In particular, they point to galantamine's

purported longer duration of action. However, in 1988, Dr. Domino himself claimed that "galanthamine is only as long acting as physostigmine but much less potent." Domino, E.F., "Galanthamine: Another Look at an Old Cholinesterase Inhibitor," in Giacobini, E., and Becker, R., eds., *Current Research in Alzheimer Therapy* 295-303 (1988) at 301(emphasis added). Any promising substitute for physostigmine in the treatment of Alzheimer's disease, where the results from physostigmine itself were, at best, small and inconsistent, would demand a more potent cholinesterase inhibitor.

48. One of ordinary skill in the art would not have been motivated to substitute galantamine for physostigmine in the treatment of Alzheimer's disease. Galantamine is chemically very different from physostigmine and tacrine with a different molecular structure which can have profound effects on pharmacologic properties and activity. Furthermore, galantamine is still a weak inhibitor of acetylcholinesterase. It is now appears that the efficacy of galantamine is due in part to its positive allosteric modulatory effect which appears to compensate for its weak cholinesterase inhibition.

49. Galantamine was also deemed by those skilled in the art as less potent than physostigmine or tacrine, making it a poor substitute for physostigmine or tacrine in treating Alzheimer's disease. The acetylcholinesterase inhibitory effect of galantamine was demonstrated 10-12 times less than that of physostigmine. Nesterenko L.N., "Effect of Galanthamine on the Acetylcholinesterase Activity of Various Regions of the Brain," Farmakologia Toksikologia, 28(4): 413-414 (1965)(translation at SYN RAZ-0013374). Tacrine was known to be about approximately 100 times more potent as an acetylcholinesterase inhibitor than galantamine. Tonkopii, V.D. et al., "Interaction of reversible inhibitors with catalytic centers and allosteric sites of cholinesterases." Bull. Exp. Biol. Med., 86:400-401

(1976)(translation at SYN RAZ-0013159-62). The literature was clear to those skilled in the art. Paskov, D.S., "Galantamine," in *New Neuromuscular Blocking Agents, Vol. 79, Handbook of Experimental Pharmacology*, Kharkevich D.A. (ed.) Springer Verlag (1986), at 654 ("The inhibitory effect of galanthamine on acetylcholinesterase . . . was found to be considerably lower than that of physostigmine and neostigmine."); D. Mihailova, et al., "Modeling of Pharmacokinetic and Pharmacodynamic Behavior of Nivalin in Anaesthetized Cats," Methods Fund. Exptl. Clin. Pharmacol., 11:595-601 (1985).

50. Those searching for a treatment for Alzheimer's disease in 1986 based on any perceived promise of physostigmine would certainly not seek a weaker cholinesterase inhibitor. The clinical studies on physostigmine, at most, taught that high levels of cholinesterase inhibition were necessary to achieve positive results in Alzheimer's patients: "Improvement on memory tests while receiving physostigmine was highly correlated with the percent of inhibition in CSF: The patients who improved up to 40% on certain memory tests had a very high degree of cholinesterase inhibition, and patients with smaller improvements also had a smaller percent of cholinesterase inhibition." Mohs et al., "Oral Physostigmine Treatment of Patients With Alzheimer's Disease," Am. J. Psychiat. 142:28-33, 32 (1985).

51. Nor would any increased duration of action have persuaded one skilled in the art to overlook galantamine's weaker cholinesterase inhibitor activity. As of January 1986, the understanding of the pharmacokinetics of galantamine was limited. The articles that did discuss its pharmacokinetics did not portray it as having a particularly long half-life. Bretagne, et al., for example, found that, at equivalently potent doses, "Galanthamine is faster in onset and more transient in duration than that of neostigmine" and reported that "[t]he Bulgarian authors who studied Galanthamine extensively showed that the action of this product persists over two

hours." Bretagne, et al., "Essis Cliniques en Anesthesiologie D'un Nouvel Anticholinesterasique la Galanthamine," Anesthesie Analgesie Reanimation, 1: 285-92 (1971) (translation at JAN RAZ-00134056-57, 134061). Yet Mohs, et al., indicated that "steady-state levels" for oral physostigmine could be achieved with 2 hour dosing. Mohs, et al., "Oral Physostigmine Treatment of Patients With Alzheimer's Disease," Am. J. Pschiat. 142: 28-33 (1985). Other researchers noted that oral physostigmine had a "much longer" duration of action than previously suspected. Thal et al., "Oral Physostigmine and Lecithin Improve Memory in Alzheimer's Disease," Ann. Neurol. 13:491-96, 495 (1983) (observing that "the biologically effective half-life of orally administered physostigmine is undoubtedly much longer than previously suspected."). Hence, in January 1986, galantamine would not have appeared clearly longer acting than physostigmine.

52. As Dr. Domino recognized in 1988, from the perspective of treating Alzheimer's disease, galantamine is simply "only as long acting as physostigmine but much less potent." (p. 301) (emphasis added). Thus, far from appearing an equivalent but longer acting version of physostigmine, as Dr. Levey and Dr. Domino suggest, galantamine would have appeared to be precisely the reverse -- as a weaker but not necessarily longer acting version of that drug.

C. Reasonable Expectation of Success

53. To a person of ordinary skill in the art in January 1986, there would not have been a reasonable expectation of success in using galantamine to treat Alzheimer's disease. Physostigmine was not seen as clinically successful and galantamine was viewed only "as long acting as physostigmine but much less potent." Furthermore, there was considerable skepticism

at the time that any cholinesterase inhibitor strategy would prove clinically successful as a treatment for Alzheimer's disease as indicated in my first report.

V. ENABLEMENT

54. I understand that to be valid, a patent must "contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention." 35 U.S.C. §112. A patent is enabling even if some experimentation is required, as long as it is not unduly extensive.

55. Dr. Domino and Dr. Levey assert that the '318 patent does not meet the "enablement" requirement of patent law because "it would not inform one of ordinary skill in the art that galantamine would be a therapeutically effective treatment for Alzheimer's disease." (Levey ¶ 120). I disagree. The '318 patent states directly that galantamine is a therapeutically effective treatment for Alzheimer's disease. It outlines an approach for Alzheimer's disease researchers to confirm the efficacy and tolerability of the invention by providing the steps appropriate for confirming Dr. Bonnie Davis' insight concerning galantamine -- most significantly, the manner of carrying out animal testing to confirm the proposed efficacy. ('318 patent col. 2:45-57).

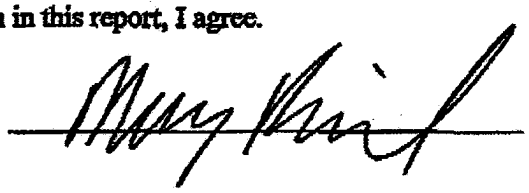
56. Dr. Levey and Dr. Domino also assert that claim 4 of the patent is not enabled because there is "no support for any dosage of galantamine at the high end of her range." (Levey ¶ 121). Again, I disagree. The patent describes the appropriate dose titration (beginning with a low dose and increasing the dose until a therapeutic response is noted or drug intolerance intervenes) to enable one skilled in the art to treat an Alzheimer's patient with galantamine.

('318 patent col. 1: 64-66). It is clear that a person of ordinary skill would be able, using standard clinical practice, to titrate doses for his or her patients so as to find a therapeutically effective dose within the claimed range.

57. Dr. Levey and Dr. Domino also suggest that Dr. Bonnie Davis did not provide the Patent Office with the necessary science in prosecuting the '318 patent. I disagree. While I am not an expert in patent prosecution and while I understand that such arguments have no relevance to anticipation, obviousness, and enablement of the '318 patent, I believe Dr. Bonnie Davis provided the Patent Office with scientifically fair and balanced information.

58. As I have already stated, The Antiseptic, let alone that particular Bhasker article, was not accessible using standard reference search techniques of those skilled in the art and would not, in any event, have been understood to relate to Alzheimer's disease at all. Additionally, she did discuss the cholinergic deficit associated with Alzheimer's disease in her patent -- in connection with describing an animal model that involved "a resultant cortical cholinergic deficiency, similar in magnitude to that seen in early to moderate stage Alzheimer's disease." ('318 patent, col. 2:48-50). And she directed the Patent Office to the scientific literature that discussed the cholinergic hypothesis and cholinesterase inhibition. Amendment Responsive to Office Action of April 10, 1986 (citing to Kendall, "Therapeutic Progress- Review XVIII Alzheimer's Disease," Journal of Clinical and Hospital Pharmacy, 10:327-36 (1985) and Hershenson and Moos, "Drug Development for Senile Cognitive Decline," Journal of Medicinal Chemistry, 29(7):1125-30 (1986)). Furthermore, Dr. Davis stated in her submission to the Patent Office that physostigmine had demonstrated "useful results" despite its poor therapeutic index and the lack of any effective treatment. As set forth in this report, I agree.

Date: September 11, 2006



ATTACHMENT A

Documents

1. "FDA Antidementia Drug Assessment Symposium," Department of Health and Human Services, Public Health Service, Food Drug Administration, Peripheral and Central Nervous System Drugs Advisory Panel (June 15, 1989)(transcript).

2. United Kingdom Patent No. 942,200

3. United States Patent No. 4,663,318

4. Letter from Frantsits and Mucke to Bonnie Davis re: galanthamine patents [SYN RAZ 0000181]

5. Letter from Bonnie Davis to Alfred Gagne re: support for claim of galanthamine's superiority in treatment of Alzheimer's disease [SYN RAZ 0017587]

6. Letter from Bonnie Davis to Dr. William Cressman re: enclosed "new set of materials on the use of galanthamine for Alzheimer's disease" [SYN RAZ 0000761 -763]

7. Shire complaint filed in Vienna Commercial Court [SYN RAZ 0018366 - 18374]]

8. Amendment [of patent application] responsive to office action of April 10 [JAN RAZ 0000031-0000039]

9. Physician's Desk Reference (2006)

10. Deposition transcript of Dr. Bonnie Davis (February 8-9, 2006) and Exhibits

Publications

1. Ashford, et al., "Physostigmine and its Effect on Six Patients," American Journal of Psychiatry, 138(6): 829-830 (1981).

2. Baraka, A, et al., "Reversal of Central Anticholinergic Syndrome by Galanthamine," JAMA, 238(21): 2293-2294 (1977).

3. Bartus, et al., "The Cholinergic Hypothesis: A Historical Overview, Current Perspective, and Future Directions," in D. Olton, et al., eds., *Annals of the New York Academy of Sciences; Memory Dysfunctions: An Integration of Animal and Human Research from Preclinical and Clinical Perspectives* 444:332-258 (1985).

4. Bartus, RT, et al., "The Cholinergic Hypothesis of Geriatric Memory Dysfunction," Science, 17: 408-417 (1982).

5. Bartus, RT, et al., "Cholinergic Treatment for Age-Related Memory Disturbances: Dead or Barely Coming of Age?" in Crook, T., *et al.*, eds., *Treatment Development Strategies for Alzheimer's Disease*, 421-450 (1986).

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11. Bretagne, M, et al., "Essais Cliniques en Anesthesiology d'un Nouvel Anticholinesterasique la Galanthamine," Anesthesie Analgesie Reanimation, 1: 285-92 (1965). (translation at JAN RAZ-00134056-57)

12. Caltagirone, et al., "Oral Administration of Chronic Physostigmine Does Not Improve Cognitive or Mnestic Performances in Alzheimer's Presenile Dementia," Intern J. Neuroscience, 16: 247-249 (1982).

13. Coyle, JT et al., "Alzheimer's Disease: a Disorder of Cortical Cholinergic Innervation," Science, 219: 1184-1190 (1983).

14. Cozanitis, DA, et al., "A Comparative Study of Galanthamine Hydrobromide and Atropine/Neostigmine in Conscious Volunteers," Anaesthesist, 20: 41 6-421 (1971).

15. Cozanitis, DA, "Galanthamine Hydrobromide Versus Neostigmine. A Plasma Cortisol Study in Man," Anaesthesia, 29(2): 163-8 (1974).

16. Cozanitis, DA, "Galanthamine Hydrobromide, a Longer Acting Anticholinesterase Drug, in the Treatment of the Central Effects of Scopolamine (Hyoscine)," Anaesthesist, 26: 649-650 (1977).

17. Cozanitis, DA, "L'hydrobromide de Galanthamine: un Substitute du Sulfate d'eserine Physystogmine) pour le Traitement des Eflets Cerebraux des Substances Anti-cholinergiques," La Nouvelle Presse Medicale, 7: 4152 (1978).

18. Cozanitis, DA, et al., "The Effect of Galanthamine Hydrobromide on Plasma ACTH in Patients Undergoing Anaesthesia and Surgery," ACTA Anaesthesiol Scand., 24(3):166-8 (1980).

19. Daskalov, D, et al., "Nivalin: Application in Rehabilitation Treatment of Cerebral Diseases with Aphasic Syndromes," MBI Medico-Biologic Information, 3: 9-11 (1980).

20. Davis, KL, et al., "Physostigmine: Improvement of Long-term Memory Processes in Normal Humans," Science, 201: 272-274 (1978).

21. Davis, KL, et al., "Enhancement of Memory Processes in Alzheimer's Disease with Multiple-dose Intravenous Physostigmine," Am J Psychiat, 139: 1421-1424 (1982).

22. Davis KL, et al., "Oral Physostigmine in Alzheimer's Disease," Psychopharmacology Bull, 19: 451-453 (1983).

23. Davis, KL, et al., "Cholinergic Drugs in Alzheimer's Disease," New England Journal of Medicine, 315(20):1286-7 (1986).

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25. Domino, EF, "Effects of Physostigmine on Rat Brain Acetylcholine, Acetylcholinesterase and Condition Pole Jumping," International Journal of Neuropharmacology (1968).

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# EXHIBIT N

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# EXHIBIT O

REDACTED

# EXHIBIT P

REDACTED

# EXHIBIT Q

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# EXHIBIT R

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## NOTICE OF ALLOWABILITY

PART I.

1. ☒ This communication is responsive to 9/11/86
2. ☒ All the claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice Of Allowance And Issue Fee Due or other appropriate communication will be sent in due course.
3. ☒ The allowed claims are 1-7
4. ☐ The drawings filed on _____ are acceptable.
5. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has [_] been received. [_] not been received. [_] been filed in parent application Serial No. _____ filed on _____
6. ☐ Note the attached Examiner's Amendment.
7. ☐ Note the attached Examiner Interview Summary Record, PTOL-413.
8. ☐ Note the attached Examiner's Statement of Reasons for Allowance.
9. ☒ Note the attached NOTICE OF REFERENCES CITED, PTO-892.
10. ☐ Note the attached INFORMATION DISCLOSURE CITATION, PTO-1449.

PART II.

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE THREE MONTHS FROM THE "DATE MAILED" indicated on this form. Failure to timely comply will result in the ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

1. ☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.
2. ☐ APPLICANT MUST MAKE THE DRAWING CHANGES INDICATED BELOW IN THE MANNER SET FORTH ON THE REVERSE SIDE OF THIS PAPER.
   a. ☐ Drawing informalities are indicated on the NOTICE RE PATENT DRAWINGS, PTO-948, attached hereto or to Paper No. _____. CORRECTION IS REQUIRED.
   b. ☐ The proposed drawing correction filed on _____ has been approved by the examiner. CORRECTION IS REQUIRED.
   c. ☐ Approved drawing corrections are described by the examiner in the attached EXAMINER'S AMENDMENT. CORRECTION IS REQUIRED.
   d. ☐ Formal drawings are now REQUIRED.

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Any response to this letter should include in the upper right hand corner, the following information from the NOTICE OF ALLOWANCE AND ISSUE FEE DUE: ISSUE BATCH NUMBER, DATE OF THE NOTICE OF ALLOWANCE, AND SERIAL NUMBER.

Attachments:

- Examiner's Amendment
- Examiner Interview Summary Record, PTOL-413
- Reasons for Allowance
- ☒ Notice of References Cited, PTO-892
- Information Disclosure Citation, PTO-1448
- _ Notice of Informal Application, PTO-152
- _ Notice re Patent Drawings, PTO-948
- _ Listing of Bonded Draftsmen
- _ Other

Stanley J. Friedman
Primary Examiner
Group Art Unit 12

PTOL-37 (REV. 3-85)